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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,669	11/08/2006	David B. Agus	67789-542	9540

50670 7590 05/19/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
05/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,669	AGUS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 20-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080220*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The election with traverse filed January 30, 2008, is acknowledged and has been entered.

Applicant has elected the invention of Group II, claims 10-19, drawn to a method of treating a condition in a mammal.

2. Claims 1-28 are pending in the application. Claims 1-9 and 20-28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 30, 2008.

3. Claims 10-19 are currently under prosecution.

Election/Restrictions

4. Applicant's traversal of the propriety of the restriction requirement set forth in the Office action mailed January 4, 2008, is acknowledged.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As evident in view of the following grounds of rejection of claim 1 under 35 U.S.C. § 102, the claim fails to link the inventions of Groups I and II by a common concept, or special technical feature, as defined by PCT Rule 13.1, because it does not define a contribution over the prior art.

Accordingly, the restriction requirement set forth in the Office action mailed January 4, 2008, is deemed proper and therefore made FINAL.

Information Disclosure Statement

5. The information disclosure filed February 20, 2008, has been considered. An initialed copy is enclosed.

Priority

6. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of PCT Application No. PCT/US04/28071, filed August 27, 2004, which claims benefit of U.S. Provisional Application No. 60/498,849, filed August 29, 2003, and U.S. Provisional Application No. 60/568,910, filed May 7, 2004, is acknowledged.

However, claims 10-19 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

In addition, it is aptly noted that neither provisional application adequately describes the claimed invention, such that either disclosure is sufficient to provide written basis for the language of the present claims. For example, neither disclosure includes a description of treating a condition in a mammal by administering a NSAID and HER2-kinase axis inhibitor on a periodic basis; additionally, neither application describes such combination therapy as inclusive of gefitinib or trastuzumab, for example; furthermore, neither application describes administering either agent sublingually, for example; and finally, neither describes administering the agents in the specific ranges recited in any of the claims. While there are still other reasons that none of the claims properly benefits from the earlier filing dates of either one of the provisional applications, it

is apparent that the differences in the scope of the disclosures in this application and those earlier applications are substantial.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely November 8, 2006.

Specification

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See M.P.E.P. § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is FuGene™; see, e.g., page 25, line 10, of the specification, as filed.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 10-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-19 are indefinite for the following reasons:

Claims 10-19 are drawn to a method of treating a "condition".

It is submitted that this recitation is not merely broad, but renders the claims indefinite for the following reasons:

It is reasonably presumed that Applicant does not regard every "condition" known to man to be treatable using the claimed invention.

At paragraph [0001], for example, of the published application[1], the specification discloses that "[e]mbodiments of the present invention are directed to methods for treating and preventing disease conditions that are modulated by the PPARγ pathway and HER-kinase axis, such as cancer".

Dorland's Illustrated Medical Dictionary[2] defines the term "cancer" as meaning "any malignant, cellular tumor, referring to neoplastic diseases in which there is a transformation of normal body cells into malignant ones"; wherein the term "tumor" is defined as: "a new growth of tissue in which cell multiplication is uncontrolled and progressive"; and the term "malignant" is defined as: "having the properties of anaplasia, invasiveness, and metastasis" (Copyright © 2007 Elsevier; Copyright © 2002-2008 Merck & Co., Inc., Whitehouse Station, NJ, USA).

Notably cancer is not defined in such a manner that it is evident that it is necessarily a disease that is modulated by the PPARγ pathway and HER-kinase axis.

In fact, cancer is a term that is used to describe any of a large number of diseases affecting a multitude of different cells and/or tissues; and such different types of cancer have markedly different etiologies and pathologies.

It is therefore not evident how "cancer" might be fairly regarded as representative of the genus of "conditions" that are treated using the claimed invention.

Besides, at paragraph [0019] of the published application, the specification discloses that the term "condition" may include, but is in no way limited to cancer.

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[1] U.S. Patent Application Publication No. 2007/0104714 A1.
[2] Available on the Internet at:
http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000016439.htm.

Which conditions are modulated by the PPARγ pathway and HER-kinase axis? How does one determine which conditions are disease conditions that are modulated by the PPARγ pathway and HER-kinase axis? What does "modulated by the PPARγ pathway and HER-kinase axis" mean?

How is cancer considered representative of such "conditions", which might be reasonably read as encompassing any minor or major affliction of the body of the mammal, such as an abrasion, a muscle ache, sleepiness, or a disease?

In addition, the claims are directed to "HER2-kinase axis inhibitors", but as explained in the written description rejection that follows, it is not evident which agents are "HER2-kinase axis inhibitors" and which are not.

There appears to be no common feature among those particularly named "HER2-kinase axis inhibitors". Many of those listed in claim 12, for example, either have no particular function (e.g., an antibody) or have substantially different and/or unrelated functions. For example, rapamycin is an immunosuppressive macrolide antibiotic, which inhibits T- and B-cell proliferation; but imatinib mesylate is 2-phenylaminopyrimidine derivative that inhibits the autophosphorylation of tyrosine kinases, such as Abl. Gelfitinib (ZD1839), on the other hand, is a selective inhibitor of epidermal growth factor receptor (EGFR); and trastuzumab is a humanized antibody that binds to the extracellular domain of HER2.

Given such disparity, the "HER2-kinase axis inhibitor" might be any substance that could be administered to a mammal in combination with a NSAID on a periodic basis, but presumably Applicant does not consider such broad subject matter to be the invention; so, rather than broad, it appears that the use of the term "HER2-kinase axis inhibitor" renders the claims indefinite.

It is submitted that rather than just broad, the claims are indefinite because there is simply no means of ascertaining the metes and bounds of the subject matter that is regarded as the invention; and consequently, it is submitted that the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter that is encompassed by the claims, so as to permit

the skilled artisan to know or determine infringing subject matter and/or non-infringing subject matter.

What is the “HER-kinase axis”? What is an “axis”? Is the “axis” a biochemical pathway? How is an "axis" different from a "pathway"?

How are members of this “axis” known or identified? How are other proteins distinguished from its members?

Is a ”HER-kinase axis inhibitor” a substance that inhibits the “axis”, as a whole, or merely a substance that inhibits an activity of one of the constituent members of the "axis"?

Again, given the obvious differences in the structures and functions of those substances that are identified with particularity in the specification (e.g., trastuzumab and rapamycin), it is submitted that the answers to these questions cannot be gleaned from the disclosure, which fails to define these terms that are used in the claims to delineate the metes and bounds of the subject matter that is regarded as the invention.

As a consequence, the claims do not delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

In accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

> 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent “conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.” Because claims delineate the patentee’s right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) (“[T]he primary purpose of the requirement is ‘to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.’”) (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that “[t]he statutory requirement of particularity

> and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in

> terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to a method of treating a “condition” in a mammal, said method comprising administering a quantity of a non-steroidal anti-inflammatory drug (NSAID) and a quantity of a "HER2-kinase axis inhibitor", both on a periodic basis.

(a) The claims are directed to a genus of “conditions”, which are too inadequately described with the requisite clarity and particularity to permit the skilled artisan to immediately envision, recognize or distinguish at least a substantial number of the members of this genus, so as to know when the invention can or cannot be used to achieve the claimed objective. As a consequence the disclosure would not reasonably convey to the skilled artisan

that Applicant had possession of the claimed invention at the time the application was filed.

At paragraph [0001], for example, of the published application, the specification discloses that "[e]mbodiments of the present invention are directed to methods for treating and preventing disease conditions that are modulated by the PPARγ pathway and HER-kinase axis, such as cancer".

Dorland's Illustrated Medical Dictionary[3] defines the term "cancer" as meaning "any malignant, cellular tumor, referring to neoplastic diseases in which there is a transformation of normal body cells into malignant ones"; wherein the term "tumor" is defined as: "a new growth of tissue in which cell multiplication is uncontrolled and progressive"; and the term "malignant" is defined as: "having the properties of anaplasia, invasiveness, and metastasis" (Copyright © 2007 Elsevier; Copyright © 2002-2008 Merck & Co., Inc., Whitehouse Station, NJ, USA).

Notably cancer is not defined in such a manner that it is evident that it is necessarily a disease that is modulated by the PPARγ pathway and HER-kinase axis.

In fact, cancer is a term that is used to describe any of a large number of diseases affecting a multitude of different cells and/or tissues; and such different types of cancer have markedly different etiologies and pathologies.

It is therefore not evident how "cancer" might be fairly regarded as representative of the genus of "conditions" that are treated using the claimed invention.

Besides, at paragraph [0019] of the published application, the specification discloses that the term "condition" may include, but is in no way limited to cancer.

Furthermore, it is not immediately evident how the conditions to which the claims might be directed are "modulated by the PPARγ pathway and HER-kinase axis", particularly since it is not clear what constitutes the pathway or the "axis",

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[3] Available on the Internet at: http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000016439.htm.

or by what nature or manner either the pathway or axis, or constituents thereof, modulate the condition.

There is simply no means of knowing which conditions or disease conditions are those to which the claims are directed. Since the "condition" to which the claims are directed is not identifiable, the invention cannot be used to achieve the claimed objective.

Applicant is reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

"Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding a sample of the "cancer" that is suitable for use in practicing the claimed invention to achieve the claimed objective; without such a sample, it is impossible to practice the invention.

There is no means of knowing whether the claimed invention can be used to treat a "condition", and thus achieve the claimed objective, if the "condition" that must be treated cannot be not known or recognized; moreover, there is simply no way to predict which of the multitude of etiologically and/or pathologically disparate diseases to which the claims might broadly, but reasonably directed in light of the disclosure, are those that are effectively treated in accordance with the process steps recited in the claims.

Although this issue is addressed again in the following paragraphs, it is aptly noted that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v.*

Lederman, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Accordingly, the specification fails to describe the genus of "conditions" with the requisite clarity and particularity to permit the skilled artisan to immediately envision, recognize or distinguish at least a substantial number of the members of this genus.

Finally, although the skilled artisan could potentially identify the different types of "conditions" (e.g., types of cancer, or other diseases) that might be applicable in the practice of the claimed invention by establishing which can be treated using the combination of agents to which the claims are directed, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

So, in summary, as a consequence of the inadequate description of the genus of "conditions" to which the claims are directed, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

(b) As another point to be addressed, it is further noted that the claims are drawn to a quantity of a non-steroidal anti-inflammatory drug (NSAID) and a quantity of a "HER2-kinase axis inhibitor".

With regard to the written description requirement, it is pertinent that terms used in the claims to describe the agents that are administered to the mammal serve to identify the agents with clarity and particularity.

Although non-steroidal anti-inflammatory agents (NSAIDs) are well known in the art, it is submitted that the genus of "HER2-kinase axis inhibitors" is not.

According to paragraph [0027] of the published application, the "HER2-kinase axis inhibitor" is any of a number of structurally and/or functionally unrelated agents, including, for example, a monoclonal antibody, rapamycin, or a tyrosine kinase inhibitor.

Notably, the monoclonal antibody need not bind any particular antigen; and the tyrosine kinase inhibitor need not inhibit the activity of any particular kinase.

Given that members of genus of "HER2-kinase axis inhibitors" have such different structures and/or functions, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the different agents to which the claims are directed.

Despite some non-limiting guidance in paragraph [0027] of the published application, for example, it is not evident which structural and/or functional features serve to identify the "HER2-kinase axis inhibitor", or which structural and/or functional features serve to distinguish members of genus of such agents from others.

Even in light of the disclosures at paragraph [0027], for example, of the published application, it is submitted that the "HER2-kinase axis inhibitors" that are used in practicing the claimed invention are not adequately described with the requisite clarity and particularity to permit the skilled artisan to know which agents those are.

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a catalog of "HER2-kinase axis inhibitors" that might be applicable in practicing the claimed invention to achieve the claimed objective does not fulfill the written description requirement.

Notably, the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, e.g., the ability to treat a condition, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004).

The claimed method depends upon finding a "HER2-kinase axis inhibitor" that can be used in the practice of the claimed invention, so that the claimed objective might be met; without the "HER2-kinase axis inhibitor", it is impossible to practice the invention.

Guidelines states, “[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was ‘ready for patenting’ such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention” (*Id.* at 1104). Moreover, because the claims encompass a genus of "HER2-kinase axis inhibitors", which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number

of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was “ready for patenting” by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Apart from any of the particularly described "HER2-kinase axis inhibitors" (e.g., rapamycin), the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed genus of agents, or of the claimed invention.

It is submitted that the genus of "HER2-kinase axis inhibitors" to which the claims are directed is too inadequately described to satisfy the written description requirement.

Then, with regard to the NSAIDs to which the claims are directed, although the prior art describes a large number of such drugs, many of those are not the equivalents of others, having different structures and/or functions, including, for example, different selectivities in terms of their abilities to inhibit either cyclooxygenase-1 (COX1) or cyclooxygenase-2 (COX1), or both COX1 and COX2, so it is not immediately evident which NSAIDs can be used in combination with the "HER2-kinase axis inhibitors" to treat a condition, particularly since the “conditions” that are treated are so very different. It stands to reason that only some NSAIDs might be used effectively in combination with only some members of the genus of "HER2-kinase axis inhibitors" to treat only some of the conditions to which the claims are directed.

For all of these reasons, it is submitted that the claims fail to satisfy the written description requirement, since the disclosure of the claimed invention

would not reasonably convey to the skilled artisan that Applicant had possession of the claimed subject matter at the time the application was filed.

12. Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims under 35 U.S.C. § 112, first and second paragraphs, the claims are directed to a method of treating any member of a genus of “conditions” using a combination of a NSAID and any member of a genus of substances termed the "HER2-kinase axis inhibitors".

Given the vast differences in the breadth of the claims and that of the guidance, direction and exemplification that is set forth in this application, it is apparent that the claimed process could not be practiced without undue and/or unreasonable experimentation.

While there are a great many reasons that this is the case, among such reasons, it is noted that the claims are directed to a "HER2-kinase axis inhibitors", which are not known or disclosed; and it cannot be predicted which agents can and cannot be considered "HER2-kinase axis inhibitors". Without that knowledge the "HER2-kinase axis inhibitor" the claimed invention cannot be used.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. “Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.” *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to elaborate upon the disclosure to develop a process that is encompassed by the claims, which can be used as intended to treat a condition using a combination of a NSAID and this other substance that has been termed the "HER2-kinase axis inhibitor".

Defining a substance by its principal biological activity, or its suitability for use in practicing the claimed process amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

As explained in the above rejection of the claims as failing to satisfy the written description requirement, it is submitted that apart from any of the particularly described "HER2-kinase axis inhibitors" (e.g., rapamycin), the disclosure fails to adequately describe these agents; of course, what has not been described cannot be made; and then what cannot be made cannot be used, certainly not without undue and unreasonable experimentation.

So can rapamycin, for example, be used in combination with a NSIAD to treat a condition?

The only disclosure that is specifically relevant to this embodiment of the claimed invention is that of the original claim 12 and the paragraph at page 13, lines 8-30, which lists rapamycin along with the generic monoclonal antibody lacking any particular binding specificity as examples of the agents that might be used as "HER2-kinase axis inhibitors".

There is no other disclosure in the specification that pertains to this embodiment.

The use of this embodiment has not been exemplified.

Rapamycin (sirolimus) is an immunosuppressive macrolide antibiotic with structural similarity to FK506, which inhibits T- and B-cell proliferation at a later stage than FK506. More particularly, rapamycin inhibits mTOR, which participates in the Ras/MAP kinase signaling pathway. Rapamycin inhibits mTOR by through association with its intracellular receptor FKBP12. Because of its immunosuppressive properties, rapamycin has been used to prevent rejection of organ and bone marrow transplants by the body; however, because mTOR regulates cell growth, cell proliferation, cell motility, cell survival, protein

synthesis, and transcription via the Ras/MAP signaling pathway, recent investigations have explored the effectiveness of rapamycin in treating cancer.

While it may be obvious to combine rapamycin with any other anticancer agent (e.g., a NSAID) to determine if the combination is more effective than either agent alone to treat a given condition[4], there does not appear to be any indication in the prior art that the combination of rapamycin and any particular NSAID should be used to treat cancer, for example, or graft versus host disease or any other condition; and, as mentioned, the specification, provides little or no guidance and direction, apart from the mere disclosure that rapamycin may be considered a member of the genus of "HER2-kinase axis inhibitors" to which the claims are directed.

Only recently have any investigations provided actual data indicating that the combination of rapamycin and a NSAID, namely celecoxib (an inhibitor of COX2) has additive antitumor effects (i.e., the combination of drugs more effectively inhibit melanoma cell growth than either drug alone)[5]. However, Applicant is reminded that supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See M.P.E.P. § 2164.05(a).

Similarly, while there may indeed be recently acquired evidence that certain combinations of a particularly described member of the genus of "HER2-kinase axis inhibitors" (e.g., monoclonal antibody 2C4; gelfitinib; and imatinib mesylate) and a NSAID are effective to treat conditions or diseases, which are generally different types of cancer, it appears that the specification, at best, might only provide guidance and direction sufficient to reasonably enable the skilled artisan to treat prostate cancer with a regimen of the NSAID, R-etodolac in

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[4] It is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition that is to be used for the very same purpose. The idea of combining the first and second compositions to form a third flows logically from having the first and second been individually taught in the prior art. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980); see M.P.E.P. § 2144.06.

[5] Bundscherer et al. (*Oncol. Rep.* 2008 Feb; **19** (2): 547-553); see entire document (e.g., the abstract).

combination with recombinant humanized monoclonal anti-HER2 antibody 2C4 (rh2C4); see, e.g., paragraphs [0076] of the published application. However, none of the claims are so limited, and since such a showing is most certainly not reasonably commensurate in scope with far broader claims, which are directed to a method of treating any "condition", not prostate cancer, by administering to a mammal afflicted with this condition an amount of any "non-steroidal anti-inflammatory drug", not R-etodolac, and an amount of a "HER2-kinase axis inhibitor", not rh2C4, the amount of guidance, direction and exemplification would not be adequate to enable the skilled artisan to use the claimed invention without undue and unreasonable experimentation.

It is important to note that not all NSAIDs act in the same ways; some are inhibitors of COX2, but others are not; and some are trans-activators of PPARγ, but others are not. Thus, if R-etodolac acts in concert with the "HER2-kinase axis inhibitor" by trans-activating PPARγ[6] to more effectively inhibit the growth of prostate cancer cells, then it follows that not all NSAIDs can be paired with a "HER2-kinase axis inhibitor" and expected to be produce additive antitumor effects.

S-etolodac, the entantiomer of R-etodolac selectively inhibits COX2, whereas R-etodolac does not. Thus, despite having such similar structures, the enantiomers have markedly different activities.

Can it be presumed that the disclosed process for inhibiting prostate cancer cells can be used, as claimed, by substituting S-etolodac for R-etodolac or any other NSAID?

Hedvat et al. (*Cancer Cell* 2004 Jun; **5**: 565-574) teaches that S-etodolac is capable of trans-activating PPARγ, but to significantly lower levels; see entire document (e.g., the abstract).

Might not the much poorer ability of S-etodolac to trans-activate PPARγ cause the drug to act ineffectively in combination with the "HER2-kinase axis

[6] R-etolodac does not inhibit COX2.

inhibitor", or might not the combination be no more effective than either one of the agents alone?

The answers to these questions are not provided in the disclosure; and the skilled artisan has no means by which the outcomes may be predicted.

In each case, the outcome of using different combinations of a NSAID and a "HER2-kinase axis inhibitor" must be determined empirically in pre-clinical or clinical trials.

Of course, since drugs often have many different effects and mechanisms of action, it is entirely possible that the antitumor activity of R-etodolac results from an effect that is independent of its ability to trans-activate PPARγ.

Curcumin (diferuloylmethane), for example, has been shown to act in combination with other antitumor drugs. Curcumin might be considered a "pharmaceutical equivalent" of the NSAID to which the claims are directed since it inhibits the activity of COX2 and trans-activates PPARγ, but curcumin has also been shown to inhibit the activation of mTOR and NF-kappaB.

Might not one of the other specific activities of a NSAID, such as curcumin account for any additive or synergistic effect that might be observed when used in combination with any given member of the genus of "HER2-kinase axis inhibitor"?

How can one know without first performing a series of highly complex experiments?

Regardless of the answer, it is apparent that the claimed invention cannot be practiced to achieve the claimed objective without undue and unreasonable experimentation.

Notably, too, there are substantial overlaps in the effects that are produced by members of the genus of "HER2-kinase axis inhibitors" and the different NSAIDs to which the claims are directed, which further blurs the features that might serve to guide the artisan to select a combination that is used effectively to treat a condition. For example, both curcumin, an agonist of PPARγ, and a presumed functional equivalent of the claimed NSAID, and

rapamycin act to inhibit the activation of mTOR; but numerous other similarities have been noted, which cause the Examiner to ponder whether the claim might not be anticipated by a showing in the prior art that administering a single therapeutic agent having properties of both the "NSAID" and the “HER2-kinase axis inhibitor" treats a condition.

Nonetheless, it is for the reasons set forth in the paragraphs above that Applicant is reminded of the following:

It is well known that the art of drug discovery for is highly unpredictable. With particular regard to anticancer drug discovery, Gura (*Science.* 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that “xenograft tumors don’t behave like naturally occurring tumors in humans” (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, “the results of xenograft screening turned out to be not much better than those obtained with the original models”. Gura states that as a result of their efforts, “ ‘[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs’ ”.

Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that

while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant

application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Bergers et al. (*Current Opinion in Genetics and Development.* 2000; **10**: 120-127) comments upon the inability to extrapolate preclinical data to reliably predict the outcome of treating humans using drugs tested in mice, particularly matrix metalloproteinase inhibitors. Bergers et al. teaches:

> A body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2).

In fact, Bergers et al. discloses that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, paragraph bridging columns 1 and 2).

Most recently, Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) reports, despite their present indispensableness, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a "laundry list" of problems associated with the use of mice to model human diseases, such as cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore, quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

Thus, the skilled artisan cannot accurately and reliably predict the effect of administering a pharmaceutical composition comprising an agent purported to have a desired pharmacological effect to a subject. Always the therapeutic effectiveness or efficacy of any unproven drug regimen can only be determined empirically.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Mitsiades et al. (*Semin. Oncol.* 2003 Apr; 30 (2): 309-312).

Here, the claims are drawn to a process of treating Waldenstrom's macroglobulinemia, said process comprising administering to a human afflicted with the condition a quantity of a peroxisome proliferator-activated receptor gamma (PPARγ) agonist and a quantity of an ansamycin.

Absent a showing of any difference, a PPARγ agonist, such as R-etodolac or rosiglitazone, is deemed the same as a non-steroidal anti-inflammatory drug (NSAID) or pharmaceutical equivalent thereof. This position is supported throughout the specification, which discloses, for example, that the NSAID is “R-

etodolac or a R-etodolac derivative, but may also include, without limitation, [...] pharmaceutical equivalents, derivatives and salts, as well as other functionally related compounds" (paragraph [0026] of the published application) and that R-etodolac activates PPARγ (e.g., paragraph [0026] and [0066]-[0070] of the published application).

Mitsiades et al. teaches a process of treating Waldenstrom's macroglobulinemia (WM), said process comprising administering to a human afflicted with the condition a quantity of a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, such as ciglitazone or rosiglitizone) and a quantity of an ansamycin, such as geldanamycin and its analogues; see entire document (e.g., the abstract). Mitsiades et al. teaches their preclinical data show that these classes of agents induce growth arrest and apoptosis of WM cells, and at concentrations relevant to those achieved in previous clinical uses of these same drugs (abstract).

Although the claims recite a limitation that the agents are administered on a "periodic basis", according to the specification, "periodically," as used in this application, "includes, but is in no way limited to, any interval of time" (paragraph [0035] of the published application). Then, the terms "NSAID periodic basis" and "HER-kinase axis inhibitor periodic basis" are consistently defined to mean including, but is in no way limited to any interval of time as would be recognized by one skilled in the art (paragraph [0035] of the published application). As such, the recitation of the limitation has little effect in defining the subject matter that is encompassed by the claims since the agents might be administered only once, or more than once at any given interval of time, and either together or separately; but then few treatment regimens involve the single administration of one or another drug, either when used alone or in combination, so it is expected that any appropriate interval of time between repeated administrations of the drugs described by the prior art would, in fact, be recognized by one skilled in the art.

15. Claims 10-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hedvat et al. (*Cancer Cell.* 2004 Jun; **5**: 565-574).

Here, the claims are drawn to a process of treating prostate cancer, said process comprising administering to a mammal afflicted with the condition a quantity of R-etolodac and a quantity of antibody 2C4.

Hedvat et al. teaches treating prostate cancer by administering to a mammal afflicted with the condition a quantity of R-etolodac and a quantity of a recombinant humanized antibody, which is designated 2C4; see entire document (e.g., the abstract). Hedvat et al. teaches the combination regimen consisted of daily administration of 200 mg/kg R-etodolac by oral gavage and twice weekly administration of 20 mg/kg antibody 2C4 by intraperitoneal injection; see, e.g., page 572, column 1.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsiades et al. (*Semin. Oncol.* 2003 Apr; 30 (2): 309-312).

Mitsiades et al. teaches that which is set forth in the above rejection of claims 10-12 under 35 U.S.C. § 102(b), but does not address the specific regimen according to which the drugs are administered, nor expressly suggests that the quantity of the peroxisome proliferator-activated receptor gamma (PPARγ) agonist is from about 100 to about 500 mg/kg of the mammal, or that it is administered daily, or that the quantity of the ansamycin is from about 100 to about 500 mg/kg, or that each drug is administered twice weekly, or that it is administered twice weekly.

The claims, however, are not limited to any one particular drug, but rather to a class of drugs having equivalent functions; and similarly the prior art teaches the effectiveness of combinations of different classes of drugs to treat the condition. In light of such permissible variance, it seems that the doses, schedules, and routes of delivery that are used in practicing the process that is claimed, and the process that is disclosed by the prior art, will vary.

It is a common objective in the art to establish a dose, schedule, and route of delivery that is both safe and effective, so as achieve optimal therapeutic effect and maximal benefit. See *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." (citations omitted)). See *In re Peterson*, 65 USPQ2d 1379 1382 (CA FC 2003): "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."

Then, with particular regard to claim 19, although the prior art does not expressly teach how each agent is administered, it is evident that the agents are delivered in accordance with their prior clinical uses, as discussed by Mitsiades et al., which absent a showing otherwise, is a delivery technique that is the same as one or more of those indicated in the claim (e.g., intravenous, sublingual, or intramuscular). Different members of the classes of drugs (i.e., the peroxisome proliferator-activated receptor gamma (PPARγ) agonist and the ansamycins) are likely administered in a plurality of different ways depending upon their formulation and pharmacokinetic properties, but in each case the route is expected to have been determined suitable, safe, and effective.

Thus, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have determined the most appropriate doses, schedules, and routes of administration, so as to practice the disclosed process of treating the condition as effectively as possible. One

ordinarily skilled in the art at the time the invention was made to do so to optimize the effectiveness of the treatment.

Absent a showing of any unobvious differences, it is therefore submitted that the process disclosed by the prior art would render obvious the process that is claimed.

This position is reasonable since parameters such as dosing, scheduling and routes of delivery, which are used to treat any given condition, may be expected to differ from those that are used most effectively to treat another condition. In general, these parameters that are used most efficaciously can only be determined in clinical trials designed to determine those parameters. The Office, however, does not have the facilities or resources for conducting clinical trials to determine if therapeutic agents are used effectively in particular regimens, as in accordance with the claims; so, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed process is different than that taught and/or suggested by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Conclusion

18. No claim is allowed.

19. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Moreover, each of such additional references that are cited on the attached PTO-Form 892 teaches and/or suggests the claimed process.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

slr
May 14, 2008